submission of this response however, the Assistant Commissioner is hereby authorized to charge any deficiency or credit any overpayment to **Deposit Account No. 50-0540.**

REMARKS

Claims 32-43 are pending in this application.

1. The Examiner has rejected claims 32-43 under 35 C.F.R. § 103(a) as being unpatentable over Malek et al. (U.S. Patent No. 5,130,238) in view of Kenten et al (U.S. Patent 6,174,709).

Applicants respectfully traverse. Malek et al. (Malek) does not teach or suggest the presently claimed subject matter. Malek merely teaches a few variations of the NASBA protocol. There is nothing in the disclosure of Malek that teaches or suggests that an ECL probe can be used in NASBA amplification. Moreover, Malek does not teach or suggest the desirability of using ECL probes..

Applicants submit that Kenten et al. (Kenten) does not compensate for the deficiencies of Malek. More specifically, Kenten does not teach or suggest the use of ECL probes in NASBA amplification. Although Kenten discloses the use of ECL probes in PCR-based single primer amplification, the differences between NASBA and PCR reactions are substantial and the ordinary skilled artisan would not reasonably expect that the successful incorporation of ECL technology with one technique would be a good predictor of success with the other.

As stated on page 2 of the specification, the invention does not require sample pretreatment, such as binding to solid phases, denaturation or purification and the probes can be added directly to the amplification mixture, hybridized and analyzed. The fact that the assay samples of the invention do not require pretreatment before the probes are added to the

amplification mixture is surprising and unexpected. This is because, at a minimum, the probe sequence could be modified by the very enzymes and components required in the amplification medium. With the simultaneous presence of three separate enzymes (i.e., reverse transcriptase, RNase H, and an RNA polymerase) in the assay, there is a much greater likelihood of unwanted side reactions taking place without pretreatment of the sample to remove contaminants. By contrast, PCR assays use a much simpler mix of enzymes that are less likely to interfere with the reaction and require, at a minimum, denaturation of the double stranded product.

In addition, the PCR reaction results in a DNA product, while NASBA results in an RNA product. A person of ordinary skill in the art would expect hybridization efficiencies to RNA in an isothermal system to be quite low, especially when two hybridizations are required, because of the lack of a denaturation step and the complex structure and folding of RNA molecules known in the art. The intramolecular hybridization within the RNA strand makes hybridization to external probes more difficult. In addition, the lower stability of RNA relative to DNA might have been expected to negatively interfere with the detection of the amplification product.

Furthermore, Applicants submit that the preferred embodiment of the invention (the detection of unlabeled amplification products through the use of two probes, one having an ECL label and the other having a capture moiety) is not disclosed in the Malek or Kenten references (alone or in combination). In contrast, Kenten discloses the combination of a labeled primer and a single labeled probe.

Applicants also submit that the Examiner takes a citation from Kenten out of context. Kenten teaches a single primer amplification, where the amplification is expected to be linear and not exponential. The unexpected exponential character of the single primer PCR

amplification in Kenten cannot be viewed as a suggestion or motivation to combine probes from Kenten with NASBA amplification of Malek.

Therefore, Applicants urge that there is no suggestion or motivation to combine the teachings of Malek with the teachings of Kenten. The Examiner fails to provide the required factual support to establish a prima facie case of obviousness. The suggestion to combine the elements must come from the reference cited and not from the applicant's disclosure. See *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). To establish prima facie obviousness based on a combination of references, the Examiner is required to demonstrate that the prior art provide "a reason, suggestion, or motivation to lead an inventor to combine those references." *Pro-Mold and Tool Co. v. Great Lakes Plastics Inc.*, 75 F.3d 1568, 1573, 37 U.S.P.Q.2d 1626, 1629 (Fed. Cir. 1996).

> [E]vidence of a suggestion, teaching, or motivation to combine may flow from the prior art references themselves, the knowledge of one of ordinary skill in the art, or in some cases, from nature of the problem solved. ... The range of sources available, however, **does not diminish the requirements for actual evidence. That is, the showing must be clear and particular**.

In re Dembiczak, 175 F.3d 994, 999, 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999) (Citation omitted, emphasis added).

Applicants respectfully maintain that Malek and Kenten, either taken alone or in combination, do not provide guidance or motivation for the successful use of ECL technology with NASBA technology. Therefore, the rejection under 35 U.S.C. § 103(a) is improper and should be withdrawn.

Favorable reconsideration of this application is respectfully requested.

Respectfully submitted,

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